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Medical Staff Conference

Myasthenia Gravis and the Thymus Gland

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SHOHET:* *Medical Grand Rounds this morning will be given by Dr. Robert Layzer, Associate Professor of Neurology. Dr. Layzer is in charge of both the Muscle Clinic and the Neurology Clinic, and he is going to talk about the role of the thymus gland in myasthenia gravis.*

DR. LAYZER:† Thank you. In order to illustrate the role of the thymus gland in myasthenia gravis, I would like to present the case of a patient whom we saw at this hospital. Mrs. Y is a 52-year-old woman who consulted me in September, 1972, because of difficulty swallowing, which had persisted for about two years. She also complained that her speech was nasal and hard to understand. There had been no ptosis or diplopia. A diagnosis of myasthenia gravis had been made, and the patient had been treated with anticholinesterase medicines. There was response to treatment at first, but as time went by it became increasingly difficult for the patient to maintain necessary nutrition. One month before admission to the hospital, while she was in Europe, the symptoms worsened and the patient began to lose weight. Returning home, she entered this hospital on September 25, 1972.

On examination the findings were restricted to the cranial nerves. There was mild weakness of the face and tongue. She was able to close her jaws strongly, but her voice was nasal, she was not able to swallow without choking and liquids sometimes came out of her nose. Adjustment of the dosage of anticholinesterase medicines did not help, and nasogastric tube feeding was required. Accordingly, about one month after admission, surgical removal of the thymus gland was carried out. The thymus gland had a normal gross appearance but contained an excessive amount of lymphocytic tissue in the form of germinal centers. After the operation there was improvement for a few days but then nasogastric feedings again were required. Prednisone was given in doses of 100 mg and 50 mg on alternate days. Within a few days the patient began to improve, and after two weeks there were almost no signs of myasthenia. She left the hospital and over the next year the dose of prednisone was gradually reduced. The

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myasthenic symptoms remained in abeyance, and the patient has been living an extremely active life without treatment for one year.

There are three major topics to be considered in a discussion of myasthenia gravis. One is the nature of the neurophysiological defect; for instance, whether the neuromuscular block is presynaptic or postsynaptic. We will not discuss that question this morning. The second topic, which will be the focus of my comments, is the pathogenesis of myasthenia, and particularly its relationship to an abnormality of the thymus gland; why removal of the thymus gland may be followed by improvement, and what is the role of disturbed immune mechanisms in myasthenia. The third topic, which I will touch on briefly, is the treatment of myasthenia gravis, a subject that relates closely to the problem of pathogenesis.

TABLE 1.—*Overall Results of Thymectomy in 267 Patients Without Thymoma Followed for Between 1 and 28 Years after Operation**

	Men		Women		Total	
Results	*Number*	*Per-cent*	*Number*	*Per-cent*	*Number*	*Per-cent*
Remission	15	30	77	36	92	35
Improvement	19	38	90	42	109	41
No change	6	12	13	6	19	7
Worse	2	4	3	1	5	2
Died	7	14	31	14	38	14
Lost to follow-up	1	2	2	1	4	1
Totals	50		217		267	

*Reproduced by permission from Perlo VP, et al.[1]

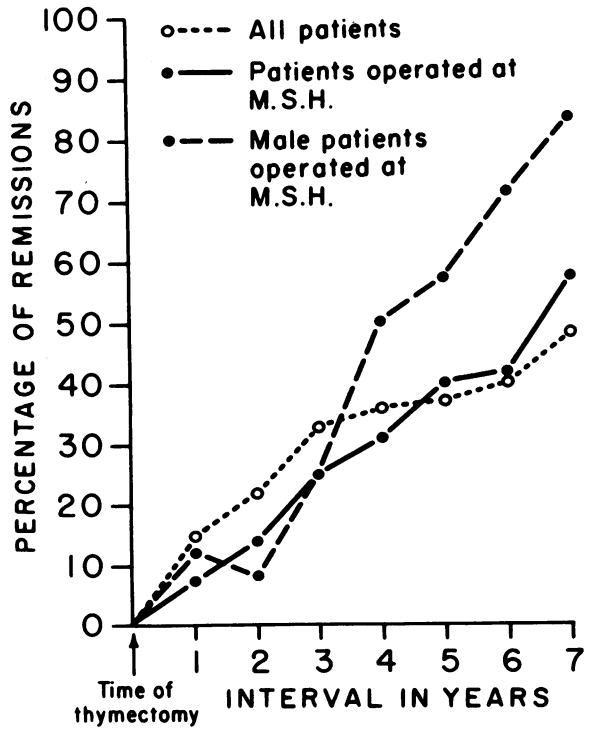

Chart 1.—Percentage of remissions in the first seven years after thymectomy. (Reproduced by permission from Papatestas AE, et al.[2])

The disease myasthenia gravis was given clinical definition in the 1870's and 1880's. Soon afterward, in 1910, Laquer and Weigert found a thymoma, a tumor of the thymus gland, in a postmortem examination of a patient with myasthenia. In 1911, Sauerbruch carried out a thymectomy for the treatment of thyrotoxicosis in a patient with myasthenia. Although the thyrotoxicosis did not improve, the myasthenic symptoms did. It was not until 1936, however, that Blalock revived interest in thymectomy in myasthenia gravis by removing a thymoma from a patient with myasthenia and noticing that the myasthenia improved. Blalock was encouraged to repeat the operation in other patients, and in 1944 he reported the results of 20 thymectomies in patients with myasthenia gravis. Most of the patients improved, and only two had tumors of the thymus gland. Since that time thymectomy has been done increasingly and with increasing confidence in patients with myasthenia gravis. In the past 20 years, thanks to improved methods of postoperative care, especially through the use of respiratory care units, thymectomy has become a relatively safe procedure.

Unfortunately, when we try to assess the results of thymectomy, we are hampered by the fact that no controlled study has ever been done and probably never will be done. Nevertheless, there is general agreement that patients treated by thymectomy fare better than untreated ones. Table 1 shows the combined results of thymectomy in 267 myasthenic patients without thymoma from the Massachusetts General Hospital and the Mt. Sinai Hospital of New York, who were followed for periods from 1 to 28 years.[1] Seventy-six percent of patients improved, with remission in nearly half of them. The death rate was 14 percent, mostly in the first four years and mostly in patients who had severe myasthenia initially. Some of the old generalizations about which patients were likely to benefit from thymectomy have not been sustained. Neither age, sex nor the duration of symptoms before surgical operation seem to affect the outcome. However, there are few statistics for patients over the age of 50, and operation is not usually recommended in patients over the age of 60 without a thymoma. The operative mortality

from thymectomy is close to zero in experienced centers.

Chart 1 shows a curious feature of the remissions that occur after thymectomy—the percentage of patients in remission increases for at least seven years after operation. (The data are from the Mt. Sinai Hospital.[2]) About 50 percent of survivors were in remission seven years after operation. The combined results from the Massachusetts General Hospital and Mt. Sinai Hospital show that remissions continue to occur even up to ten years after operation.[1] On the other hand, only 10 percent of patients go into remission in the first postoperative year.

In view of these results, it seems appropriate to do thymectomy in myasthenia whenever the disease is sufficiently disabling to warrant it. A patient should have more than purely ocular myasthenia, should not be older than about 60 years and should have good general health. It seems reasonable that surgical operation be done early because improvement may be delayed for many years.

The technique of thymectomy should be mentioned here. In some hospitals the sternum-splitting approach, which has been standard for many years, has been replaced by the less traumatic transcervical approach with results said to be just as good.[2] Nevertheless, in this hospital we still use the older method, feeling that it gives better visualization with less risk of leaving thymic tissue behind.

What is this mysterious benefit that takes seven years to reach a 50-percent remission rate and rarely produces remission in the first year? What is the role of the thymus in myasthenia? The answers are not yet available, but let us review some of the evidence at hand. First of all, thymoma is strongly linked to myasthenia. This tumor occurs in about 10 percent of all patients with myasthenia. Looking at it the other way around, 30 percent of patients with thymoma have myasthenia gravis, although this figure is a little weighted because patients with myasthenia are carefully scrutinized for the presence of thymoma. Table 2 lists some other diseases associated with thymoma. Some of these diseases also occur in association with each other, and each of them has appeared at one time or another in association with both myasthenia and thymoma, except for Cushing's syndrome. But myasthenia is rarely linked with these other diseases, and the lymphoepithelial type of tumor found in myasthenia is not the type usually associated with other diseases.

TABLE 2.—*Disorders Sometimes Associated with Thymoma*

Myasthenia Gravis
Aregenerative Anemia (Leukopenia, Thrombocytopenia)
Hypogammaglobulinemia
Cushing's Syndrome
Pemphigus
Autoimmune Hemolytic Anemia
Lupus Erythematosus and Other Connective Tissue Diseases
Polymyositis, Myocarditis
Chronic Mucocutaneous Candidiasis

In patients with myasthenia in whom there is not a tumor, the thymus often shows abnormal proliferation of the lymphoid elements with formation of germinal centers in the thymic medulla, a change which has been termed thymic hyperplasia.[3] Germinal centers have been said not to occur in normal thymic tissue, but in an autopsy study of patients who died in accidents, 70 percent of thymuses showed at least one germinal center.[4] However, germinal centers are more numerous in the thymic medulla in persons with myasthenia than in normal persons; they have also been found in lupus erythematosus and in other connective tissue diseases.[5] In elderly patients with myasthenia the thymus gland often does not contain any recognizable thymic tissue.[6]

Thus, myasthenia is strongly linked with frank pathology of the thymus gland. Why, then, does it take so long before a patient benefits from thymectomy? Why is removal of a neoplastic thymus gland less often followed by improvement than removal of a nontumorous gland? Why does myasthenia sometimes appear for the first time *after* a tumor of the thymus gland has been removed, even a year or two later?[7] These questions still have not been answered satisfactorily. Several hypotheses have been put forward to account for the role of the thymus in myasthenia, and we can examine these in turn.

An early idea was that the thymus secreted a substance that caused myasthenia. Support for this idea came from the clinical observation that 10 to 30 percent of the babies born to mothers with myasthenia suffer from neonatal myasthenia for a few weeks after birth. This neonatal myasthenia is always transient. It is difficult to escape the conclusion that some circulating maternal substance crosses the placenta to cause myasthenia in the baby, but the substance, if it exists, has proved to be very elusive.

During the 1940's, Andrew Wilson in England obtained, from both human and whale thymus glands, small amounts of a substance that produced neuromuscular block, but this research came to nothing (although a similar achievement, as we will see, was recently reported by Goldstein). In 1960, Simpson in Scotland announced the novel hypothesis that myasthenia is an autoimmune disease.[8] Simpson pointed out an association between myasthenia and other diseases suspected to have an autoimmune pathogenesis, such as rheumatoid arthritis and pernicious anemia. (Rowland and his colleagues, on the other hand, found that myasthenia is rarely associated with other diseases except for the well-known association with thyrotoxicosis.[9]) Simpson suggested that myasthenia might be caused by circulating antibodies against the acetylcholine receptor in the motor end plate. Curiously enough, just at that time Nastuk at Columbia University, with a medical student named Arthur Strauss, was looking for a neuromuscular blocking substance in myasthenic serum. They discovered that some myasthenic sera had a cytopathic effect on their muscle preparations. Nastuk and Strauss subsequently identified the cytopathic serum factor as an antibody.[10] With the fluorescent antibody technique, these antibodies react with the cross striations of skeletal muscle; by electron microscopy it appears that the antibodies react with sarcoplasmic reticulum at the I bands. This kind of antibody is present in the serum of 30 percent of patients with myasthenia who do not have a thymoma, but is found in the serum of almost all patients with myasthenia who do have a thymoma. It is also present in a quarter of patients with thymoma who do not have myasthenia.[11] The reason that muscle antibodies occur in patients with thymoma was suggested by the discovery that these antibodies also react with certain cells in the thymus called myoid cells.[12] As their name suggests, these muscle-like cells have cross striations, contain myofibrils and are, in effect, little muscle cells.

Here then is another important link between myasthenia and the thymus—antibodies that cross-react with muscle and thymus. Unfortunately, the antibodies do not seem to be the right kind to cause myasthenia. In the first place, they do not seem to be the factor that crosses the placenta to cause neonatal myasthenia, for they may be absent from the serum of the mothers who have babies with neonatal myasthenia, and may be present in mothers who give birth to unaffected babies.[13] Second, the antibodies do not react with the end plate region of muscle, the site of altered function in myasthenia. Attempts to detect antibody bound to the neuromuscular junction in myasthenia have also been unsuccessful.[14]

In the laboratory, however, an interesting experimental model of myasthenia was recently produced by immunizing rabbits with purified acetylcholine receptor prepared from the electric organ of Electrophorus electricus. In the rabbits, antibodies against the acetylcholine receptor were produced, and these antibodies blocked the rabbits' own receptors, causing severe weakness that could be reversed by administration of anticholinesterase drugs.[15] In these elegant experiments, the antibody can be likened to pharmacological agents like curare or bungarotoxin, which also react specifically with the acetylcholine receptor and produce weakness. Several laboratories are now searching for similar antibodies in serum from patients with myasthenia.[16]

As knowledge of immune mechanisms increased, another autoimmune theory of myasthenia became current. It was proposed that myasthenia is a disease of cellular immunity, and that a clone of immune lymphocytes somehow produces the neuromuscular block. This mechanism could explain why the effect of thymectomy may be delayed for so long, since lymphocytes which are capable of causing disease may remain in circulation after thymectomy. The role of the thymus in initiating or perpetuating the disease might then be correlated with the known function of the thymus in regulating the immune function of lymphocytes. There is little direct evidence for this theory, but support recently has been provided by two reports describing the effects of prolonged thoracic duct lymph drainage in five patients with myasthenia.[17,18] All five patients improved, some of them strikingly, and weakness returned a few days after the procedure was stopped. The pathogenetic role of lymphocytes in myasthenia needs to be better defined.

Finally, I would like to describe the Goldstein hypothesis.[19] Gideon Goldstein suggested that the pathology of the thymus gland in myasthenia resembled that of autoimmune thyroiditis (Hashimoto's disease). He called this process autoimmune thymitis, and he suggested that the damaged thymus gland leaked a protein substance (not an antibody) into the blood and that this substance was capable of causing neuromuscular block. To support this theory, he produced an experimental

model by immunizing animals with thymus gland and testing neuromuscular transmission by repetitive nerve stimulation. He reported that immunized animals showed an abnormal decline in the amplitude of evoked muscle action potentials although the animals did not become weak. Several other investigators have been unable to reproduce these results, and Goldstein's theory has therefore not met with wide acceptance. Recently Goldstein isolated from the thymus tissue two polypeptides (which he named thymin I and II) said to have neuromuscular blocking properties. When these peptides were assayed for their ability to produce neuromuscular blockade, it appeared that 4 μg of thymin reduced the evoked muscle action potential to about 85 percent of the initial value, but larger amounts of thymin caused no further decline in response.[20] This dose response curve is difficult to interpret and casts doubt on the relevance of thymin to the pathogenesis of myasthenia although the peptides appear to have some influence on immune mechanisms.

Despite tantalizing hints, therefore, we do not really understand the role of the thymus in myasthenia or why some patients take so long to benefit from thymectomy. In seriously ill patients who have not responded to thymectomy, we are left with one other form of treatment, the one that was used in Mrs. Y's case, glucocorticosteroid therapy. High doses of corticosteroid medication produce excellent remission of weakness in nearly all cases, and usually the dose can be reduced in time to a tolerable maintenance level. If possible, it is best to carry out thymectomy before using steroids in order to improve the likelihood of achieving permanent remission. Of course, steroid therapy is a two-edged sword and should only be given to patients whose myasthenia is sufficiently disabling or life-threatening to warrant the risks of such treatment.

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